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(54) Title: ANTIVIRAL COMPOSITIONS

(57) Abstract: The present invention is concerned with pharmaceutical compositions of antiviral compounds which can be administered to a mammal, in particular a human, suffering from a viral infection. These compositions comprise particles obtainable by melt-extruding a mixture comprising one or more antiviral compounds and one or more appropriate water-soluble polymers and subsequently milling said melt-extruded mixture.

# ANTIVIRAL COMPOSITIONS

The present invention concerns pharmaceutical compositions of antiviral compounds which can be administered to a mammal, in particular a human, suffering from a viral infection. These compositions comprise particles obtainable by melt-extruding a mixture comprising one or more antiviral compounds and one or more appropriate water-soluble polymers and subsequently milling said melt-extruded mixture.

The antiviral compounds constituting the pharmaceutical compositions of the present invention are dispersed in a carrier by melt-extrusion to obtain a solid dispersion in order to improve their bio-availability.

Compounds structurally related to the present antiviral compounds are disclosed in the prior art.

Pharmazie (1990), 45(4), p 284 discloses trisubstituted derivatives of 2,4,6-trichloro-1,3,5-triazine having anti-bacterial activity.

Chem. Abstr. (1990), 112, no. 1 concerns synthesis of fluorinated derivatives of 1,3,5-triazine as potential bactericidal agents.

Chem. Abstr. (1988), 108, no. 15 describes 2,4,6-mixed functional substituted 1,3,5-triazines as anti-convulsives.

Chem. Abstr. (1983), 98, no. 11 concerns the preparation of *p*-(2,4-diarylamino-6-S-triazinylamino)-benzaldehyde/acetophenone thiosemicarbazones as potential tuberculostatic agents.

Chem. Abstr. (1981), 95, no. 4 describes the preparation of polypyromellitimides containing dialkylamino-type melamine units.

Chem. Abstr. (1975), 83, no. 23 describes optically active S-triazine derivatives.

FR-A-2099730 concerns diamino-, and dinitro-S-triazines, which can be used for the preparation of polymeric material and colorants.

EP-A-0795549 discloses bis-aryloxy(amino)-triazinyl-oxy(amino)aryl derivatives as antiviral agents.

Ashley et al. (J. Chem. Soc. (1960), January 1, pp 4525-4532) describes amidinoanilino-1,3,5-triazines having potential trypanocidal activity.

WO 91/18887 discloses diaminopyrimidines as gastric acid secretion inhibitors.

EP-A-0588762 concerns the use of *N*-phenyl-2-pyrimidinamine derivatives as proteinkinase C-inhibitors and anticancer agents.

WO 95/10506 describes *N*-alkyl-*N*-aryl-pyrimidinamines and derivatives thereof as Corticotropin Releasing Factor receptor antagonists.

EP-A-0270111 discloses pyrimidine derivatives as fungicides in agricultural and horticultural compositions.

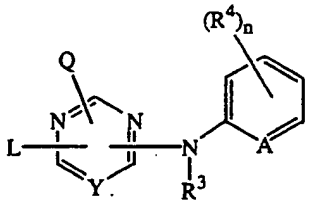
J. Med. Chem. (1969), 10, pp 974-975 describes 2,4-bis(arylamino)-5-methyl-pyrimidines and Chem. Abstr. (1981), 95, no. 11 describes 2,4-bis(arylamino)-6-methylpyrimidines as antimicrobial agents.

J. Med. Chem. (1996), 39, pp 4358-4360 deals with 4-anilino-6-aminopyrimidines as non-peptide high affinity human Cortocotropin Releasing Factor$_1$ receptor antagonists.

EP-0,834,507 discloses substituted diamino 1,3,5-triazine derivatives having HIV replication inhibiting properties.

The particles of the present invention consist of a solid dispersion comprising

(a) an antiviral compound of formula



(I-A)

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is $CR^5$ or N;

A is CH, $CR^4$ or N;

n is 0, 1, 2, 3 or 4;

Q is $-NR^1R^2$ or when Y is $CR^5$ then Q may also be hydrogen;

$R^1$ and $R^2$ are each independently selected from hydrogen, hydroxy, $C_{1-12}$alkyl, $C_{1-12}$alkyloxy, $C_{1-12}$alkylcarbonyl, $C_{1-12}$alkyloxycarbonyl, aryl, amino, mono- or di($C_{1-12}$alkyl)amino, mono- or di($C_{1-12}$alkyl)aminocarbonyl wherein each of the aforementioned $C_{1-12}$alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, $C_{1-6}$alkyloxy, hydroxy$C_{1-6}$alkyloxy, carboxyl, $C_{1-6}$alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di($C_{1-6}$alkyl)amino, aryl and Het; or

$R^1$ and $R^2$ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di($C_{1-12}$alkyl)amino$C_{1-4}$alkylidene;

$R^3$ is hydrogen, aryl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyl, $C_{1-6}$alkyloxycarbonyl, $C_{1-6}$alkyl substituted with $C_{1-6}$alkyloxycarbonyl; and

each $R^4$ independently is hydroxy, halo, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, cyano, amino

carbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is $CR^5$ then $R^4$ may also represent $C_{1-6}$alkyl substituted with cyano or aminocarbonyl;

$R^5$ is hydrogen or $C_{1-4}$alkyl;

L is $-X^1-R^6$ or $-X^2$-Alk-$R^7$ wherein

$R^6$ and $R^7$ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is $CR^5$ then $R^6$ and $R^7$ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then $R^6$ and $R^7$ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; when $R^6$ is optionally substituted indanyl or indolyl, it is preferably attached to the remainder of the molecule via the fused phenyl ring. For instance, $R^6$ is suitably 4-, 5-, 6- or 7-indolyl;

$X^1$ and $X^2$ are each independently $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$;

Alk is $C_{1-4}$alkanediyl; or

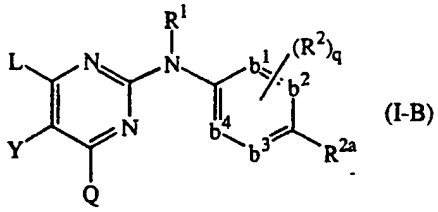
when Y is $CR^5$ then L may also be selected from $C_{1-10}$alkyl, $C_{3-10}$alkenyl, $C_{3-10}$alkynyl, $C_{3-7}$cycloalkyl, or $C_{1-10}$alkyl substituted with one or two substituents independently selected from $C_{3-7}$cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, cyano, aminocarbonyl, $C_{1-6}$alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and $C_{1-6}$alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

or

an antiviral compound of formula



(I-B)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

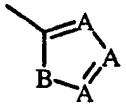
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

$R^1$ is hydrogen, aryl, formyl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyl, $C_{1-6}$alkyloxycarbonyl, $C_{1-6}$alkyl substituted with formyl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl;

$R^{2a}$ is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, $C_{1-6}$alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, $C_{2-6}$alkenyl substituted with cyano, or $C_{2-6}$alkynyl substituted with cyano;

each $R^2$ independently is hydroxy, halo, $C_{1-6}$alkyl optionally substituted with cyano or $-C(=O)R^6$, $C_{3-7}$cycloalkyl, $C_{2-6}$alkenyl optionally substituted with one or more halogen atoms or cyano, $C_{2-6}$alkynyl optionally substituted with one or more halogen atoms or cyano, $C_{1-6}$alkyloxy, $C_{1-6}$alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di($C_{1-6}$alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A independently is N, CH or $CR^6$;

B is NH, O, S or $NR^6$;

p is 1 or 2; and

$R^6$ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{3-7}$cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* $C_{3-7}$cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and $C_{1-6}$alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in $R^2$; or

L is -X-$R^3$ wherein

$R^3$ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in $R^2$; and

X is -$NR^1$-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -$S(=O)_2$-;

Q represents hydrogen, $C_{1-6}$alkyl, halo, polyhalo$C_{1-6}$alkyl or -$NR^4R^5$; and

$R^4$ and $R^5$ are each independently selected from hydrogen, hydroxy, $C_{1-12}$alkyl, $C_{1-12}$alkyloxy, $C_{1-12}$alkylcarbonyl, $C_{1-12}$alkyloxycarbonyl, aryl, amino, mono- or di($C_{1-12}$alkyl)amino, mono- or di($C_{1-12}$alkyl)aminocarbonyl wherein each of the aforementioned $C_{1-12}$alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, $C_{1-6}$alkyloxy, hydroxy$C_{1-6}$alkyloxy, carboxyl, $C_{1-6}$alkyloxycarbonyl, cyano, amino, imino, mono- or di($C_{1-6}$alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -$S(=O)_pR^6$, -NH-$S(=O)_pR^6$, -$C(=O)R^6$, -NHC(=O)H, -$C(=O)NHNH_2$, -$NHC(=O)R^6$,-$C(=NH)R^6$, aryl and Het; or

$R^4$ and $R^5$ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di($C_{1-12}$alkyl)amino$C_{1-4}$alkylidene;

Y represents hydroxy, halo, $C_{3-7}$cycloalkyl, $C_{2-6}$alkenyl optionally substituted with one or more halogen atoms, $C_{2-6}$alkynyl optionally substituted with one or more halogen atoms, $C_{1-6}$alkyl substituted with cyano or -$C(=O)R^6$, $C_{1-6}$alkyloxy, $C_{1-6}$alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di($C_{1-6}$alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -$S(=O)_pR^6$, -NH-$S(=O)_pR^6$, -$C(=O)R^6$, -NHC(=O)H, -$C(=O)NHNH_2$, -$NHC(=O)R^6$,-$C(=NH)R^6$ or aryl;

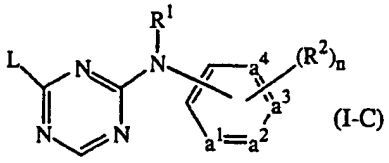
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each

independently selected from halo, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{1-6}$alkyloxy, cyano, nitro, polyhalo$C_{1-6}$alkyl and polyhalo$C_{1-6}$alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy; Het is meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het, for instance, pyrrolyl also includes 2*H*-pyrrolyl; the Het radical may be attached to the remainder of the molecule of formula (I-B) through any ring carbon or heteroatom as appropriate, thus, for example, when the heterocycle is pyridinyl, it may be 2-pyridinyl, 3-pyridinyl or 4-pyridinyl.

or

an antiviral compound of formula



(I-C)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

-N=CH-CH=N- (a-4);

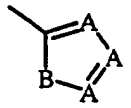
-N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

$R^1$ is hydrogen, aryl, formyl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyl, $C_{1-6}$alkyloxycarbonyl, $C_{1-6}$alkyl substituted with formyl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl; and

each $R^2$ independently is hydroxy, halo, $C_{1-6}$alkyl optionally substituted with cyano or $-C(=O)R^4$, $C_{3-7}$cycloalkyl, $C_{2-6}$alkenyl optionally substituted with one or more halogen atoms or cyano, $C_{2-6}$alkynyl optionally substituted with one or more halogen atoms or cyano, $C_{1-6}$alkyloxy, $C_{1-6}$alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di($C_{1-6}$alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,

$-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or $CR^4$;

B is NH, O, S or $NR^4$;

p is 1 or 2; and

$R^4$ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{3-7}$cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* $C_{3-7}$cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and $C_{1-6}$alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in $R^2$; or

L is $-X-R^3$ wherein

$R^3$ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in $R^2$; and

X is $-NR^1-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, $C_{1-6}$alkyloxy, cyano, nitro, polyhalo$C_{1-6}$alkyl and polyhalo$C_{1-6}$alkyloxy;

with the proviso that compounds wherein

* L is $C_{1-3}$alkyl; $R^1$ is selected from hydrogen, ethyl and methyl; $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula (a-1); n is 0 or1 and $R^2$ is selected from fluoro, chloro, methyl, trifluoromethyl, ethyloxy and nitro; or
* L is $-X-R^3$, X is -NH-; $R^1$ is hydrogen; $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula (a-1); n is 0 or1 and $R^2$ is selected from chloro, methyl, methyloxy, cyano, amino and nitro and $R^3$ is phenyl, optionally substituted with one substituent selected from chloro, methyl, methyloxy, cyano, amino and nitro;

and the compounds

* *N,N'*-dipyridinyl-(1,3,5)-triazine-2,4-diamine;
* (4-chloro-phenyl)-(4(1-(4-isobutyl-phenyl)-ethyl)-(1,3,5) triazin-2-yl)-amine

are not included;

and

(b) one or more pharmaceutically acceptable water-soluble polymers.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhalo$C_{1-6}$alkyl as a group or part of a group is defined as mono- or polyhalosubstituted $C_{1-6}$alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like; in case more than one halogen atoms are attached to an alkyl group within the definition of polyhalomethyl or polyhalo$C_{1-6}$alkyl, they may be the same or different; $C_{1-4}$alkyl as a group or part of a group encompasses the straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl and the like; $C_{1-6}$alkyl as a group or part of a group encompasses the straight and branched chained saturated hydrocarbon radicals as defined in $C_{1-4}$alkyl as well as the higher homologues thereof containing 5 or 6 carbon atoms such as, for example pentyl or hexyl; $C_{1-10}$alkyl as a group or part of a group group encompasses the straight and branched chained saturated hydrocarbon radicals as defined in $C_{1-6}$alkyl as well as the higher homologues thereof containing 7 to 10 carbon atoms such as, for example, heptyl, octyl, nonyl or decyl; $C_{1-12}$alkyl as a group or part of a group encompasses the straight and branched chained saturated hydrocarbon radicals as defined in $C_{1-10}$alkyl as well as the higher homologues thereof containing 11 or 12 carbon atoms such as, for example, undecyl, dodecyl and the like; $C_{1-4}$alkylidene as a group or part of a group defines bivalent straight and branched chained hydrocarbons having from 1 to 4 carbon atoms such as, for example, methylene, ethylidene, propylidene, butylidene and the like; $C_{1-4}$alkanediyl as a group or part of a group encompasses those radicals defined under $C_{1-4}$alkylidene as well as other bivalent straight and branched chained hydrocarbons having from 1 to 4 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; $C_{3-7}$cycloalkyl as a group or part of a group is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; $C_{3-10}$alkenyl as a group or part of a group defines straight and branch chained hydrocarbon radicals containing one double bond and having from 3 to10 carbon atoms such as, for example, 2-propenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl,

3-hexenyl, 3-heptenyl, 2-octenyl, 2-nonenyl, 2-decenyl and the like, whereby the carbon atom attached to the pyrimidine ring is preferably an aliphatic carbon atom; $C_{3-10}$alkynyl as a group or part of a group defines straight and branch chained hydrocarbon radicals containing one triple bond and having from 3 to10 carbon atoms such as, for example, 2-propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 3-methyl-2-butynyl, 3-hexynyl, 3-heptynyl, 2-octynyl, 2-nonynyl, 2-decynyl and the like, whereby the carbon atom attached to the pyrimidine ring is preferably an aliphatic carbon atom; $C_{2-6}$alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; $C_{2-10}$alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a double bond such as the groups defined for $C_{2-6}$alkenyl and heptenyl, octenyl, nonenyl, decenyl and the like; $C_{2-6}$alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; $C_{2-10}$alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a triple bond such as the groups defined for $C_{2-6}$alkynyl and heptynyl, octynyl, nonynyl, decynyl and the like; $C_{1-3}$alkyl as a group or part of a group encompasses the straight and branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as, methyl, ethyl and propyl; $C_{4-10}$alkyl encompasses the straight and branched chain saturated hydrocarbon radicals as defined above, having from 4 to 10 carbon atoms. The term $C_{1-6}$alkyloxy defines straight or branched chain saturated hydrocarbon radicals such as methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, 1-methylethyloxy, 2-methyl-propyloxy, 2-methylbutyloxy and the like; $C_{3-6}$cycloalkyloxy is generic to cyclo-propyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide group when attached once to a sulfur atom, and a sulfonyl group when attached twice to a sulfur atom.

When any variable (e.g. aryl, $R^3$, $R^4$ in formula (I-A) etc.) occurs more than one time in any constituent, each definition is independent.

Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms. For instance for compounds of formula (I-A), $R^4$ can be attached to any available carbon atom of the phenyl or pyridyl ring.

The addition salts as mentioned herein are meant to comprise the therapeutically active addition salt forms which the compounds of formula (I-A), (I-B) or (I-C) are able to form with appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The pharmaceutically acceptable addition salts as mentioned hereinabove are also meant to comprise the therapeutically active non-toxic base, in particular, a metal or amine addition salt forms which the compounds of the present invention are able to form. Said salts can conveniently be obtained by treating the compounds of the present invention containing acidic hydrogen atoms with appropriate organic and inorganic bases such as, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

The term addition salts also comprises the hydrates and the solvent addition forms which the compounds of formula (I-A), (I-B) or (I-C) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of the compounds of formula (I-A), (I-B) or (I-C), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I-A), (I-B) or (I-C) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formula (I-A), (I-B) or (I-C) may also exist in their

tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term compound of formula (I-A), (I-B) or (I-C) is meant to include any subgroup thereof, also the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and all stereoisomeric forms.

Suitable compounds of formula (I-A) are those wherein Y is $CR^5$ or N; A is CH, $CR^4$ or N; n is 0, 1, 2, 3 or 4; Q is $-NR^1R^2$; $R^1$ and $R^2$ are each independently selected from hydrogen, hydroxy, $C_{1-12}$alkyl, $C_{1-12}$alkyloxy, $C_{1-12}$alkylcarbonyl, $C_{1-12}$alkyloxycarbonyl, aryl, amino, mono- or di($C_{1-12}$alkyl)amino, mono- or di($C_{1-12}$alkyl)aminocarbonyl wherein each of the aforementioned $C_{1-12}$alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, $C_{1-6}$alkyloxy, hydroxy$C_{1-6}$alkyloxy, carboxyl, $C_{1-6}$alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di($C_{1-6}$alkyl)amino, aryl and Het; or $R^1$ and $R^2$ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di($C_{1-12}$alkyl)amino$C_{1-4}$alkylidene; $R^3$ is hydrogen, aryl, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyl, $C_{1-6}$alkyloxycarbonyl, $C_{1-6}$alkyl substituted with $C_{1-6}$alkyloxycarbonyl; each $R^4$ independently is hydroxy, halo, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy; $R^5$ is hydrogen or $C_{1-4}$alkyl; L is $-X^1-R^6$ or $-X^2$-Alk-$R^7$ wherein $R^6$ and $R^7$ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, $C_{1-6}$alkylcarbonyl, $C_{1-6}$alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl, $X^1$ and $X^2$ are each independently $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$, and Alk is $C_{1-4}$alkanediyl; aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, $C_{1-6}$alkyl, $C_{1-6}$alkyloxy, cyano, nitro and trifluoromethyl; Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

Most preferred compounds of formula (I-A) are
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-2-pyrimidinyl]amino]benzonitrile (*1.B1; comp. 1);

6-[(2,6-dichlorophenyl)methyl]-*N*2-(4-fluorophenyl)-2,4-pyrimidinediamine (*1.B1; comp. 2);

4-[[4-[(2,4-dichlorophenyl)methyl]-6-[(4-hydroxybutyl)amino]-2-pyrimidinyl]amino]-benzonitrile (*1.B2; comp. 3);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[(3-hydroxypropyl)amino]-2-pyrimidinyl]-amino]benzonitrile (*1.B1; comp. 4);

*N*-[2-[(4-cyanophenyl)amino]-6-[(2,6-dichlorophenyl)methyl]-4-pyrimidinyl]acetamide (*1.B7; comp. 5);

*N*-[2-[(4-cyanophenyl)amino]-6-[(2,6-dichlorophenyl)methyl]-4-pyrimidinyl]-butanamide (*1.B7; comp. 6);

4-[[2-amino-6-(2,6-dichlorophenoxy)-4-pyrimidinyl]amino]benzonitrile (*1.B1; comp. 7);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[(2-hydroxy-2-phenylethyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B2; comp. 8);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-2-pyrimidinyl]amino]benzonitrile (*1.B2; comp. 9);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[[2-(2-hydroxyethoxy)ethyl]amino]-2-pyrimidinyl]amino]benzontrile monohydrochloride (*1.B2; comp. 10);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[(2,3-dihydroxypropyl)amino]-2-pyrimidinyl]-amino]benzonitrile (*1.B2; comp. 11);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-2-pyrimidinyl]amino]-benzonitrile (*1.B4; comp. 12);

4-[[4-[(2-cyanoethyl)amino]-6-[(2,6-dichlorophenyl)methyl]-2-pyrimidinyl]amino]-benzonitrile (*1.B3; comp. 13);

4-[[4-[(2,6-dichlorophenyl)methyl]-6-[[2-(1-pyrrolidinyl)ethyl]amino]-2-pyrimidinyl]-amino]benzonitrile (*1.B3; comp. 14);

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-5-methyl-2-pyrimidinyl]amino]-benzonitrile (*1.B1; comp. 15);

*N*2-(4-bromophenyl)-6-[(2,6-dichlorophenyl)methyl]-5-methyl-2,4-pyrimidinediamine (*1.B1; comp. 16);

4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B8a; comp. 17);

4-[[2-[(2,4,6-trimethylphenyl)amino]-4-pyrimidinyl]amino]benzonitrile (*1.B9a; comp. 18);

4-[[4-[(2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9a; comp. 19);

4-[[4-(2,4,6-trimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (*1.B10; comp. 20);

4-[[4-[(2,6-dichlorophenyl)thio]-2-pyrimidinyl]amino]benzonitrile (*1.B10; comp. 21);
4-[[4-[[2,6-dibromo-4-(1-methylethyl)phenyl]amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9a; comp. 22);
4-[[4-[[2,6-dichloro-4-(trifluoromethyl)phenyl]amino]-2-pyrimidinyl]amino]-benzonitrile (*1.B9c; comp. 23);
4-[[4-[(2,4-dichloro-6-methylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9a; comp. 24);
4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile (*1.B8a or 1.B8b; comp. 25);
4-[[4-[(2,4-dibromo-6-fluorophenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 26);
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-5-methyl-2-pyrimidinyl]amino]-benzeneacetonitrile (*1.B1; comp. 27);
4-[[4-[methyl(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 28);
4-[[4-[(2,4,6-trichlorophenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 29);
4-[[4-[(2,4,6-trimethylphenyl)thio]-2-pyrimidinyl]amino]benzonitrile (*1.B10; comp. 30);
4-[[4-[(2,4,6-trimethylphenyl)amino-2-pyrimidinyl]amino]benzonitrile (*1.B11; comp. 31);
4-[[4-amino-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B1; comp. 32);
4-[[2-amino-6-[(2,4,6-trimethylphenyl)amino]-4-pyrimidinyl]amino]benzonitrile (*1.B1; comp. 33);
4-[[4-(2-bromo-4-chloro-6-methylphenoxy)-2-pyrimidinyl]amino]benzonitrile (*1.B10; comp. 34);
4-[[4-[(4-chloro-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 35);
3,5-dichloro-4-[[2-[(4-cyanophenyl)amino]-4-pyrimidinyl]amino]benzonitrile (*1.B9a; comp. 36);
4-[[4-[[2,6-dichloro-4-(trifluoromethoxy)phenyl]amino]-2-pyrimidinyl]amino]-benzonitrile (*1.B9c; comp. 37);
4-[[4-[(2,4-dibromo-3,6-dichlorophenyl)amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 38);
4-[[4-[(2,6-dibromo-4-propylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 39);

4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzamide (*1.B11; comp. 40);
4-[[4-[(4-(1,1-dimethylethyl)-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile (*1.B9a; comp. 41);
4-[[2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (*1.B10; comp. 42);
4-[[4-[(4-chloro-2,6-dimethylphenyl)amino]-5-methyl-2-pyrimidinyl]amino]-benzonitrile (*1.B9c; comp. 43);
4-[[2-[(4-cyanophenyl)amino]-5-methyl-4-pyrimidinyl]amino-3,5-dimethylbenzonitrile (*1.B9b; comp. 44);
4-[[4-[[4-(1,1-dimethylethyl)-2,6-dimethylphenyl]amino]-5-methyl-2-pyrimidinyl]-amino]benzonitrile (*1.B9c; comp. 45);
4-[[4-[(4-bromo-2,6-dimethylphenyl)amino]-5-methyl-2-pyrimidinyl]amino]-benzonitrile (*1.B9c; comp. 46);
4-[[5-methyl-4-[(2,4,6-trimethylphenyl)thio]-2-pyrimidinyl]amino]benzonitrile (*1.B9c; comp. 47);
4-[[4-[(2,6-dibromo-4-propylphenyl)amino]-5-methyl-2-pyrimidinyl]amino]-benzonitrile (*1.B9a; comp. 48);
4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzamide, *N*3-oxide (*1.B12; comp. 49);
*N*2-(4-chlorophenyl)-N4-(2,4,6-trimethylphenyl)-2,4-pyrimidinediamine (*1.B8a; comp. 50);
4-[[4-[[2,6-dibromo-4-(1-methylethyl)phenyl]amino]-5-methyl-2-pyrimidinyl]amino]-benzonitrile (*1.B9a; comp. 51);
4-[[2-[(4-cyanophenyl)amino]-5-methyl-4-pyrimidinyl]amino]-3,5-dimethyl Benzonitrile (*1.B9b; comp. 52);
4-[[4-[(phenylmethyl)amino]-2-pyrimidinyl]amino]benzonitrile (comp. 53);
4-[[4-amino-6-(2,6-dimethylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B15; comp. 54);
4-[[4-amino-6-[(2-chloro-6-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B13a; comp. 55);
4-[[4-amino-6-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B13a or 1.B13b; comp. 56);
4-[[4-(hydroxyamino)-6-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B14; comp. 57);
4-[[4-amino-6-[(2-ethyl-6-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B13b; comp. 58);

4-[[4-amino-6-[(2,6-dichlorophenyl)thio]-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B13b; comp. 59);
4-[[4-(hydroxyamino)-6-[(2,4,6-trichlorophenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B14; comp. 60);
4-[[4-amino-6-(2,4,6-trimethylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B13b; comp. 61);
4-[[4-(hydroxyamino)-6-(2,4,6-trimethylphenoxy)-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B14; comp. 62);
4-[[4-amino-6-[(2,4-dichloro-6-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B13b; comp. 63);
4-[[4-[(2,4-dichloro-6-methylphenyl)amino]-6-(hydroxyamino)-1,3,5-triazin-2-yl]-amino]benzontrile (*1.B14; comp. 64);
4-[[4-(hydroxyamino)-6-(2,4,6-trichlorophenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile trifluoroacetate (1:1) (*1.B14; comp. 65);
4-[[4-(4-acetyl-2,6-dimethylphenoxy)-6-amino-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B16; comp. 66);
4-[[4-amino-6-(2,4,6-tribromophenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B17; comp. 67);
4-[[4-amino-6-(4-nitro-2,6-dimethylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B17; comp. 68);
4-[[4-amino-6-(2,6-dibromo-4-methylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B17; comp. 69);
4-[[4-amino-6-(4-formyl-2,6-dimethylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B17; comp. 70);
4-[[4-amino-6-[(2,4-dichlorophenyl)thio]-1,3,5-triazin-2-yl]amino]benzonitrile (*1.B17; comp. 71);
4-[[4-[(5-acetyl-2,3-dihydro-7-methyl-1H-inden-4-yl)oxy]-6-amino-1,3,5-triazin-2-yl]-amino]benzonitrile (*1.B20; comp. 72);
4-[[4-amino-6-[(4-bromo-2-chloro-6-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B20; comp. 73);
4-[[4-amino-6-[(2-chloro-4,6-dimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B20; comp. 74);
4-[[4-amino-6-[[2,4-dichloro-6-(trifluoromethyl)phenyl]amino]-1,3,5-triazin-2-yl]-amino]benzonitrile (*1.B13; comp. 75);
4-[[4-amino-6-[methyl(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B18; comp. 76);

4-[[4-amino-6-[(2,6-dibromo-4-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile (*1.B13b; comp. 77);
4-[[4-amino-6-[[2,6-dibromo-4-(1-methylethyl)phenyl]amino]-1,3,5-triazin-2-yl]-amino]benzonitrile (*1.B13b; comp. 78);
the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof (* indicates the example number of the preparation procedure listed in the experimental part according to which the compound of formula (I-A) was synthesized).

Suitable compounds of formula (I-B) are those wherein one or more of the following restrictions apply :

i) $-b^1=b^2-C(R^{2a})=b^3-b^4=$ is a radical of formula (b-1);
ii) q is 0;
iii) $R^{2a}$ is cyano or $-C(=O)NH_2$, preferably $R^{2a}$ is cyano;
iv) Y is cyano, $-C(=O)NH_2$ or a halogen, preferably a halogen;
v) Q is hydrogen or $-NR^4R^5$ wherein $R^4$ and $R^5$ are preferably hydrogen;
vi) L is $-X-R^3$ wherein X is preferably $NR^1$, O or S, most preferably X is NH, and $R^3$ is substituted phenyl with $C_{1-6}$alkyl, halogen and cyano as preferred substituents.

Another interesting group of compounds of formula (I-B) are those compounds of formula (I-B) wherein L is $-X-R^3$ wherein $R^3$ is 2,4,6-trisubstituted phenyl, each substituent independently selected from chloro, bromo, fluoro, cyano or $C_{1-4}$alkyl.

Also interesting are those compounds of formula (I-B) wherein Y is chloro or bromo and Q is hydrogen or amino.

Particular compounds of formula (I-B) are those compounds of formula (I-B) wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group.

Preferred compounds of formula (I-B) are those compounds of formula (I-B) wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group, L is $-X-R^3$ wherein $R^3$ is a 2,4,6-trisubstituted phenyl, Y is a halogen and Q is hydrogen or $NH_2$.

Most preferred compounds of formula (I-B) are :
4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]-benzonitrile; and
4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]-benzonitrile; the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof.

An interesting group of compounds of formula (I-C) are those compounds of formula (I-C) wherein one or more of the following conditions are met :

(i) n is 1;

(ii) $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula (a-1);

(iii) $R^1$ is hydrogen or alkyl;

(iv) $R^2$ is cyano; aminocarbonyl; mono- or di(methyl)aminocarbonyl; $C_{1-6}$alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl; and more in particular, $R^2$ is on the 4 position relative to the $-NR^1-$ moiety;

i) L is $-X-R^3$ wherein X is preferably $-NR^1-$, -O- or -S-, most preferably X is -NH-, and $R^3$ is substituted phenyl with $C_{1-6}$alkyl, halogen and cyano as preferred substituents.

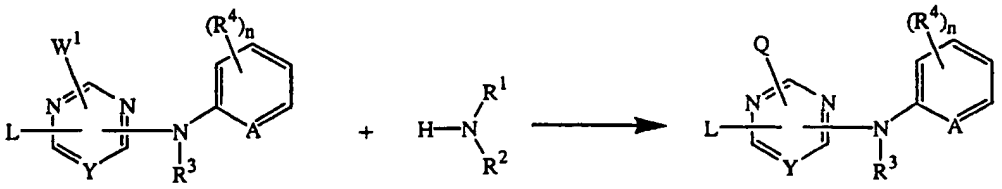
Preferred compounds of formula (I-C) are those compounds of formula (I-C) wherein L is $-X-R^3$ wherein $R^3$ is a disubstituted phenyl group or a trisubstituted phenyl group, each substituent independently selected from chloro, bromo, fluoro, cyano or $C_{1-4}$alkyl.

Most preferred compound of formula (I-C) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile .

The compounds of formula (I-A) can be prepared according to art-known procedures.

In particular, the compounds of formula (I-A) can generally be prepared by reacting an intermediate of formula (II), wherein $W^1$ is a suitable leaving group such as, for example, a halo atom with an amino derivative of formula (III) in a reaction inert solvent such as, for example, 1,4-dioxane, tetrahydrofuran, 2-propanol, *N*-methyl-pyrrolidinone and the like, optionally in the presence of a suitable base such as, for

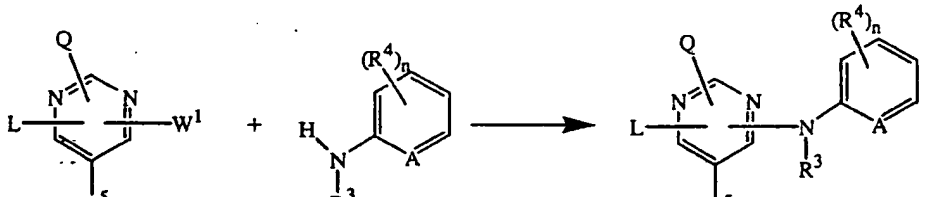
example, sodiumhydroxide, sodiumhydride, triethylamine or *N,N*-di-isopropyl-ethylamine or the like.



(II) (III) (I-A)

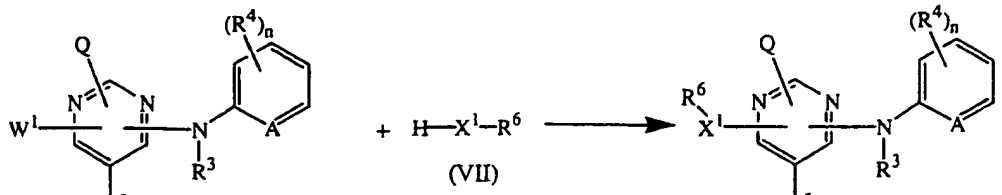
In case Q is $NR^1R^2$ and $R^2$ contains a hydroxy moiety, it may be convenient to perform the above reaction with a protected form of intermediate (III) whereby the hydroxy moiety bears a suitable protecting group P being, for instance, a benzyl, and subsequently removing the protective group according to art-known methodologies, such as, for example, reacting with $BBr_3$ in dichloromethane under nitrogen atmosphere.

Compounds of formula (I-A) wherein Y is $CR^5$, said compounds being represented by formula (I-A-a), may also be prepared by reacting an intermediate of formula (IV) wherein $W^1$ is a suitable leaving group such as, for example, a halo atom, with an amino derivative of formula (V), optionally in a solvent such as, for example, water, 2-propanol, diethylether, 1-methyl-2-pyrrolidinone and the like, and optionally in the presence of an acid such as, for example, 1 N hydrochloric acid in diethylether. It may be convenient to perform the reaction under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen.



(IV) (V) (I-A-a)

Compounds of formula (I-A-a) wherein L is $-X^1-R^6$, said compounds being represented by formula (I-A-a-1), can also be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (VII) in a suitable solvent such as, for example, 1,4-dioxane.



(VI) (VII) (I-A-a-1)

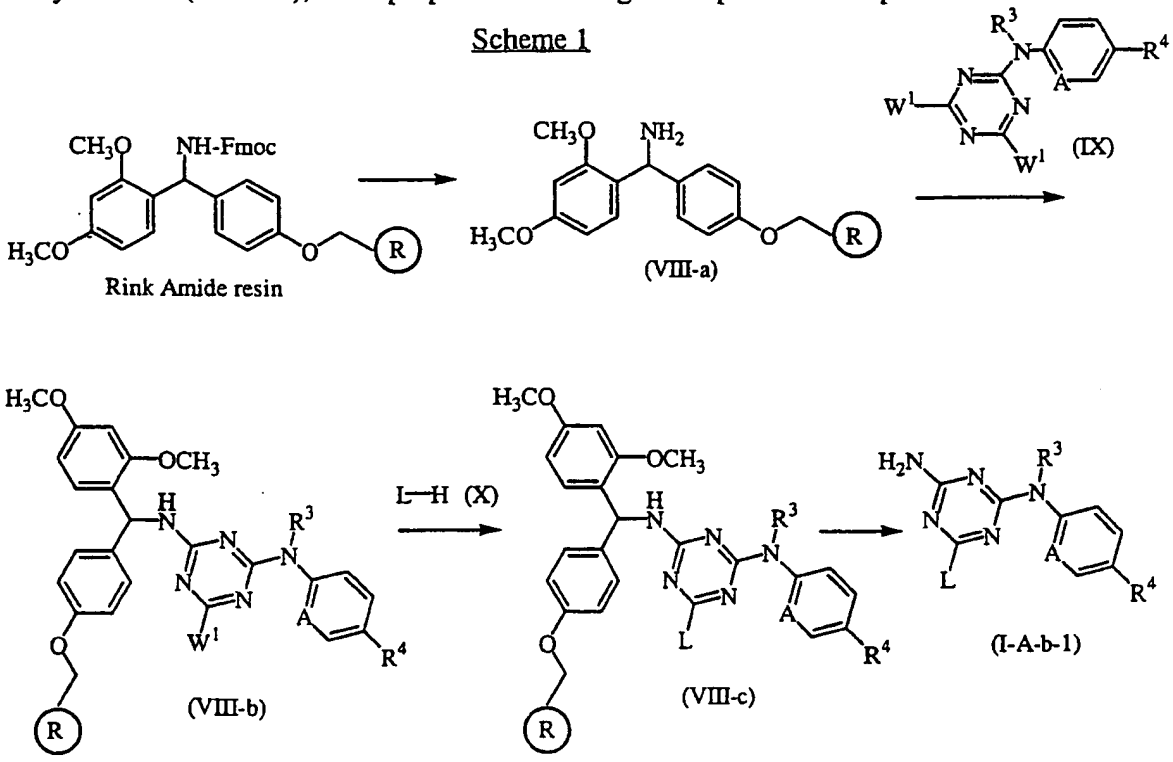
Depending on the nature of $X^1$ a suitable base or acid may be used to improve the reaction rate. For instance, in case $X^1$ is -O-, sodium hydride may be used as suitable base; or in case $X^1$ is $-NR^3-$, HCl may be used as a suitable acid.

The compounds of formula (I-A), wherein Y is N, said compounds being represented by formula (I-A-b), can also conveniently be prepared using solid phase synthesis techniques. In general, solid phase synthesis involves reacting an intermediate in a synthesis with a polymer support. This polymer supported intermediate can then be carried on through a number of synthetic steps. After each step, impurities are removed by filtering the resin and washing it numerous times with various solvents. At each step the resin can be split up to react with various intermediates in the next step thus allowing for the synthesis of a large number of compounds. After the last step in the procedure the resin is treated with a reagent or process to cleave the resin from the sample.

Suitable polymer supports include for instance Rink Amide resin (Calbiochem-Novabiochem Corp., San Diego, California).

For instance, the compounds of formula (I-A-b) wherein n is 1 and the $R^4$ substituent is placed in the meta position of A, and $NR^1R^2$ is $NH_2$, said compounds being represented by formula (I-A-b-1), were prepared according to the procedure depicted in Scheme 1.

Scheme 1



In scheme 1, Rink Amide resin is reacted in a suitable solvent such as, for example *N,N*-dimethylformamide in the presence of piperidine to obtain the primary amine of formula (VIII-a) which can then further be reacted with an intermediate of formula (IX) wherein $W^1$ is a suitable leaving group such as, for example, a halo atom, in the presence of a base such as for example, *N,N*-diisopropylethylamine, in a suitable solvent such as, for example, dimethylsulfoxide. Impurities can be removed by washing numerous times with various solvents such as, for example, *N,N*-dimethylformamide, dichloromethane, dimethylsulfoxide and the like. The resulting polymer-bound intermediate of formula (VIII-b) was then further reacted with L-H (X). To facilitate this transformation, silver triflate, sodium hexamethyldisilazide or cesium carbonate may be used. The resin is finally treated with a cleavage reagent such as for example trifluoroacetic acid in tetrahydrofuran, thus obtaining compounds of formula (I-A-b-1).

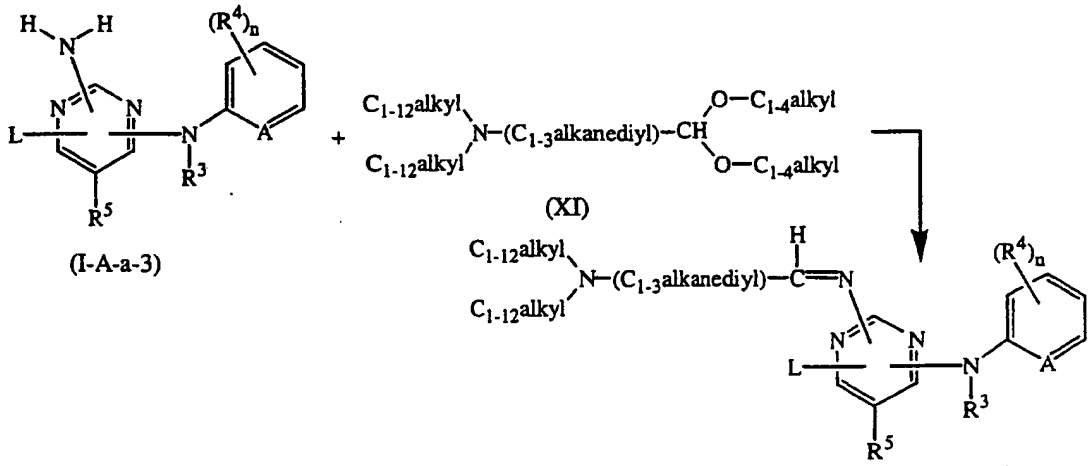
In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

The compounds of formula (I-A) may further be prepared by converting compounds of formula (I-A) into each other according to art-known group transformation reactions.

The compounds of formula (I-A) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I-A) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

For instance, compounds of formula (I-A-a) wherein Q is $NR^1R^2$ and $R^1$ and $R^2$ are taken together to form mono- or di($C_{1-12}$alkyl)amino$C_{1-4}$alkylidene, said compounds

being represented by formula (I-A-a-2), may be prepared by reacting a compound of formula (I-A-a) wherein $R^1$ and $R^2$ are hydrogen, said compound being represented by formula (I-A-a-3), with an intermediate of formula (XI) or a functional derivative thereof.




Also, compounds of formula (I-A-a) wherein Q is $NR^1R^2$ and $R^1$ and $R^2$ are hydrogen may further be reacted with an acyl halide or an alkyl chloroformate in a reaction-inert solvent such as, for example dichloromethane, in the presence of a suitable base, such as, for example, pyridine, to form the corresponding amide, respectively, carbamate derivative.

Some of the compounds of formula (I-A) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.